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(54) Title: THERAPEUTIC USES OF TRIAZOLO–PYRIDAZINE DERIVATIVES

(57) Abstract

A class of substituted or 7,8–ring fused 1,2,4–triazolo[4,3–b]pyridazine derivatives, possessing an optionally substituted cycloalkyl, phenyl or heteroaryl substituent at the 3–position and a substituted alkoxy moiety at the 6–position, are selective ligands for $GABA_A$ receptors, in particular having high affinity for the $\alpha 2$ and/or $\alpha 3$ subunit thereof, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity, e.g. in paraplegic patients.

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THERAPEUTIC USES OF TRIAZOLO-PYRIDAZINE DERIVATIVES

The present invention relates to the use of a class of substituted triazolo-pyridazine derivatives in therapy. More particularly, this invention is concerned with the use of substituted 1,2,4-triazolo[4,3-b]pyridazine derivatives which are ligands for $GABA_A$ receptors in the treatment and/or prevention of psychotic disorders including schizophrenia; neurodegeration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity, e.g. in paraplegic patients.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, three β subunits, three γ subunits and one δ subunit.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, a δ subunit also exists, but is present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of thirteen allows for the possible existence of more than 10,000 pentameric subunit

combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha2\beta\gamma1$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$, $\alpha6\beta\delta$ and $\alpha4\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha1\beta\gamma2$, $\alpha2\beta\gamma2$ or $\alpha3\beta\gamma2$ subunits will possess desirable antipsychotic, neuroprotective, analgesic, antiemetic, and muscle relaxant and/or antispastic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha2$ and/or $\alpha3$ subunit than with $\alpha1$ will be effective in the treatment of psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity; with a reduced propensity to cause sedation.

In DE-A-2741763, and in US Patents 4,260,755, 4,260,756 and 4,654,343, are described various classes of 1,2,4-triazolo[4,3-b]pyridazine derivatives which are alleged to be useful as anxiolytic agents. The compounds described in DE-A-2741763 and in US Patents 4,260,755 and 4,654,343 possess a phenyl substituent at the 6-position of the triazolo-pyridazine ring system. The compounds described in US Patent 4,260,756, meanwhile, possess a heteroaryl moiety at the 6- or 8-position. In none of these publications, however, is there any disclosure or suggestion of 1,2,4-triazolo[4,3-b]pyridazine derivatives wherein the substituent at the 6-position is attached through a directly linked oxygen atom. Moreover, these publications nowhere disclose or suggest that the compounds described therein might be an effective therapy for psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity.

EP-A-0085840 and EP-A-0134946 describe related series of 1,2,4-triazolo[3,4-a]phthalazine derivatives which are stated to possess antianxiety activity. However, there is no disclosure nor any suggestion in either of these publications of replacing the benzo moiety of the triazolo-phthalazine ring system with any other functionality. Moreover, these publications nowhere disclose or suggest that the compounds described therein might be an effective therapy for psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity.

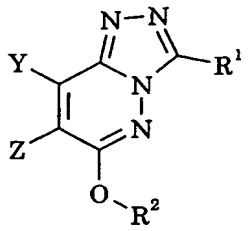
The present invention provides a new use for a class of triazolo-pyridazine derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The compounds of use in the present invention have good affinity as ligands for the α2 and/or α3 subunit of the human $GABA_A$ receptor. The compounds of use in this invention may interact more favourably with the α2 and/or α3 subunit than with the α1 subunit. Desirably, the compounds of use in the invention will exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

The compounds of use in the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the α2 and/or α3 subunit, as measured in the assay described hereinbelow, of 100 nM or less, typically of 50 nM or less, and ideally of 10 nM or less. The compounds of use in this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the α2 and/or α3 subunit relative to the α1 subunit. However, the use of compounds which are unselective in terms of their binding affinity for the α2 and/or α3 subunit relative to the α1 subunit is also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

In *J. Psychiatr. Res.*, 1996, **30**, 239-250 are presented the results of a clinical efficacy study of bretazenil, a partial benzodiazepine-receptor agonist, in schizophrenic patients with an acute psychotic episode. The results of the study are stated to suggest moderate antipsychotic efficacy of bretazenil in schizophrenic patients. The most frequent adverse reaction reported in the study was sedation, and this may be attributable to the fact that bretazenil is not a functionally selective $GABA_A$ receptor agonist in the sense that it displays comparable efficacy for the $\alpha 1$ subunit as it does for the $\alpha 2$ and/or $\alpha 3$ subunit.

In *J. Cereb. Blood Flow Metab.*, 1997, **17**, 875-883 is described a study to determine the ability of the imidazoquinoline amide derivative PNU-101017 to salvage selectively vulnerable neuronal populations in the gerbil forebrain ischemia model. PNU-101017 is stated therein to produce a dose-related increase in neuronal survival, and hence to have potential for the treatment of global cerebral ischemia. However, PNU-101017 is referred to in this publication as having high affinity for $GABA_A$ receptor subtypes containing the $\alpha 1$ and $\alpha 3$ or $\alpha 5$ subunits, being a partial agonist at each of these receptors with approximately 50% of the intrinsic activity of the full agonist diazepam. In other words, PNU-101017 is not a functionally selective $GABA_A$ receptor agonist in the sense that it displays comparable efficacy for the $\alpha 1$ subunit as it does for the $\alpha 3$ subunit. PNU-101017 can therefore be expected to suffer from the drawback of possessing the characteristic side-effect profile associated with compounds displaying appreciable $\alpha 1$ subunit agonist activity.

The present invention provides a method for the treatment and/or prevention of psychotic disorders, including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity (e.g. in paraplegic patients); which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



(I)

wherein

Y represents hydrogen or C_{1-6} alkyl; and

Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or

Y and Z are taken together with the two intervening carbon atoms to form a ring selected from C_{5-9} cycloalkenyl, C_{6-10} bicycloalkenyl, tetrahydropyridinyl, pyridinyl and phenyl, any of which rings may be optionally benzo-fused and/or substituted;

R^1 represents C_{3-7} cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted; and

R^2 represents cyano(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, propargyl, C_{3-7} heterocycloalkylcarbonyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

The present invention also provides the use of a compound of formula I as defined above, or a pharmaceutically acceptable salt thereof or a prodrug thereof, for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders, including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity (e.g. in paraplegic patients).

As used herein, the expression "neurodegeneration arising from cerebral ischemia" will be understood to include neuronal damage and

deterioration resulting from cerebral ischemic episodes which may be associated with vascular occlusion (e.g. during open heart surgery or cardiac arrest), stroke, hypoglycaemia, cerebral palsy, perinatal asphyxia, epilepsy, Huntington's chorea, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, olivo-ponto-cerebellar atrophy, anoxia (e.g. from drowning, spinal cord injury or head injury), subarachnoid haemorrhage, and poisoning by exogenous and endogenous excitatory neurotoxins, including environmental neurotoxins.

As used herein, the term "pain" comprises pain and nociception. The compounds of use in the present invention will accordingly be beneficial in the therapy of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, dental pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain (for example odontalgia), abdominal pain, and gynaecological pain (for example dysmenorrhoea and labour pain); pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; lower back pain; sciatica; ankylosing spondylitis; gout; and scar pain.

As used herein, the term "emesis" will be understood to include nausea and vomiting. The compounds of use in the present invention are beneficial in the therapy of acute, delayed or anticipatory emesis, including emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders (e.g. motion sickness, vertigo, dizziness and Meniere's disease), surgery, migraine, and

variations in intracranial pressure. The compounds of use in the invention are of particular benefit in the therapy of emesis induced by radiation, for example during the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting. Most especially, the compounds of use in the invention are beneficial in the therapy of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy, and emesis induced by other pharmacological agents, for example rolipram.

Examples of such chemotherapeutic agents include alkylating agents, for example nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D.J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, ed. J. Kucharczyk *et al.*, CRC Press Inc., Boca Raton, Florida, USA, 1991, pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil (R.J. Gralle *et al.* in *Cancer Treatment Reports*, 1984, 68, 163-172).

Where Y and Z are taken together with the two intervening carbon atoms to form a ring, the resulting compounds of formula I above incorporate the relevant cycloalkenyl, bicycloalkenyl, tetrahydropyridinyl, pyridinyl or phenyl ring fused to the central triazolo-pyridazine ring system as depicted in formula I.

Where Y and Z are taken together with the two intervening carbon atoms to form a C_{5-9} cycloalkenyl ring, this ring may be a cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl or cyclononenyl ring, suitably cyclohexenyl or cycloheptenyl.

Where Y and Z are taken together with the two intervening carbon atoms to form a C_{6-10} bicycloalkenyl ring, this ring may be a bicyclo[2.1.1]hex-2-enyl, bicyclo[2.2.1]hept-2-enyl, bicyclo[2.2.2]oct-2-enyl, bicyclo[3.2.2]non-6-enyl or bicyclo[3.3.2]dec-9-enyl ring, suitably bicyclo[2.2.1]hept-2-enyl, bicyclo[2.2.2]oct-2-enyl or bicyclo[3.2.2]non-6-enyl, and especially bicyclo[2.2.2]oct-2-enyl.

Where Y and Z are taken together with the two intervening carbon atoms to form a ring, this ring may be optionally benzo-fused. By way of illustration, Y and Z taken together with the two intervening carbon atoms may represent a benzo-fused cyclohexenyl ring, whereby the resulting ring is dihydronaphthyl.

The groups Y, Z, R^1 and R^2 may be unsubstituted, or substituted by one or more, suitably by one or two, substituents. In general, the groups Y, Z, R^1 and R^2 will be unsubstituted or monosubstituted. Examples of optional substituents on the groups Y, Z, R^1 and R^2 include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, C_{3-7} cycloalkoxy, amino(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl, morpholinyl(C_{1-6})alkyl, di(C_{1-6})alkylmorpholinyl(C_{1-6})alkyl and imidazolyl(C_{1-6})alkyl.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl and 1,1-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy" are to be construed accordingly.

Typical C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The expression "C_{3-7} cycloalkyl(C_{1-6})alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

Typical C_{4-7} cycloalkenyl groups include cyclobutenyl, cyclopentenyl and cyclohexenyl.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their

pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of use in this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of use in the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of use in the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope the use of prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds of use in the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds of use in the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that the use of all such isomers and mixtures thereof in any proportion is encompassed within the scope of the present invention.

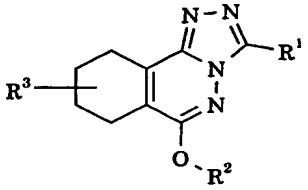
Suitably, Y represents hydrogen or methyl, especially hydrogen.

Examples of suitable values for the substituent Z include methyl, ethyl, isopropyl, *tert*-butyl, 1,1-dimethylpropyl, methyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, cyclobutenyl, phenyl, pyrrolidinyl, methyl-pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, pyridinyl, furyl, thienyl, chloro-thienyl and diethylamino.

In a particular embodiment, the substituent Z represents C_{3-7} cycloalkyl, either unsubstituted or substituted by C_{1-6} alkyl, especially methyl. Favourably, Z represents cyclobutyl.

When Y and Z are taken together with the two intervening carbon atoms to form a ring, representative compounds of use in the invention include those of structure IA to IL, especially IA to IK:



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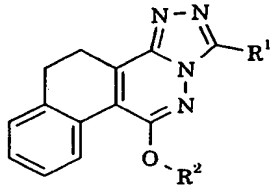

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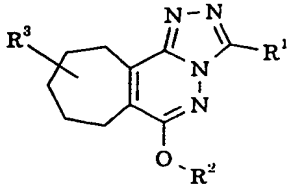

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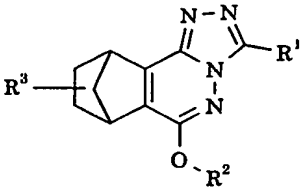

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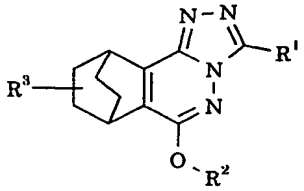

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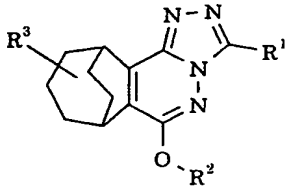

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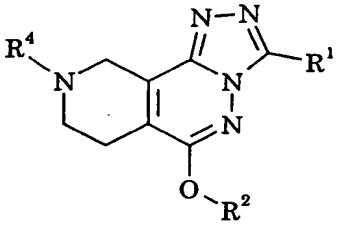

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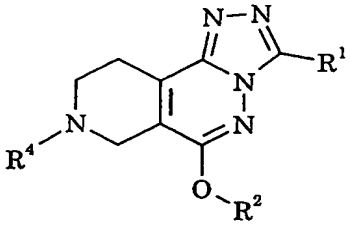

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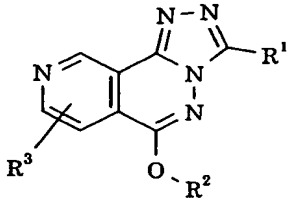

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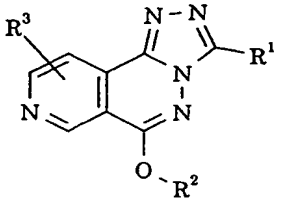

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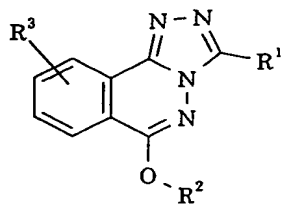


(IL)

wherein R^1 and R^2 are as defined above;

R^3 represents hydrogen, C_{1-6} alkyl, aryl(C_{1-6})alkyl, halogen, cyano, hydroxy, hydroxymethyl or C_{1-6} alkoxy; and

R^4 represents hydrogen or C_{1-6} alkyl.

Suitably, R^3 represents hydrogen or C_{1-6} alkyl, especially hydrogen or methyl.

Suitably, R^4 represents hydrogen or methyl.

Favoured triazolo-pyridazine derivatives of use in the present invention include the compounds represented by formula IE as depicted above.

Examples of typical optional substituents on the group R^1 include methyl, fluoro and methoxy.

Representative values of R^1 include cyclopropyl, phenyl, methylphenyl, fluorophenyl, difluorophenyl, methoxyphenyl, furyl, thienyl, methyl-thienyl and pyridinyl. Particular values include cyclopropyl, phenyl, methylphenyl, fluorophenyl, methoxyphenyl and pyridinyl. More particularly, R^1 may represent unsubstituted or monosubstituted phenyl. Most particularly, R^1 represents phenyl.

Suitable values for the substituent R^2 in the compounds of use in the invention include cyanomethyl, hydroxybutyl, cyclohexylmethyl, propargyl, pyrrolidinylcarbonylmethyl, benzyl, pyrazolylmethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, benzimidazolylmethyl, oxadiazolylmethyl, triazolylmethyl, tetrazolylmethyl, pyridinylmethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Examples of suitable optional substituents on the group R^2 include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxymethyl, C_{1-6} alkoxy, C_{3-7}

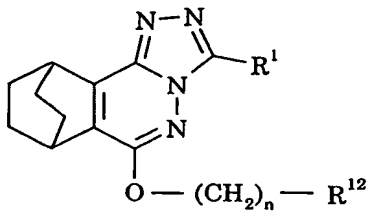
cycloalkyl(C_{1-6})alkoxy, amino(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl, morpholinyl(C_{1-6})alkyl and di(C_{1-6})alkylmorpholinyl(C_{1-6})alkyl.

Specific illustrations of particular substituents on the group R^2 include methyl, ethyl, *n*-propyl, benzyl, pyridinylmethyl, chloro, chloromethyl, cyano, cyanomethyl, hydroxymethyl, ethoxy, cyclopropylmethoxy, dimethylaminomethyl, aminoethyl, dimethylaminoethyl, dimethylaminocarbonylmethyl, *N*-methylpiperidinyl, pyrrolidinylethyl, piperazinylethyl, morpholinylmethyl and dimethylmorpholinylmethyl.

Representative values of R^2 include cyanomethyl, hydroxybutyl, hydroxymethyl-cyclohexylmethyl, propargyl, dimethylaminomethyl-propargyl, dimethylmorpholinylmethyl-propargyl, pyrrolidinylcarbonylmethyl, cyanobenzyl, hydroxymethyl-benzyl, pyrazolylmethyl, dimethyl-pyrazolylmethyl, methyl-isoxazolylmethyl, thiazolylmethyl, methyl-thiazolylmethyl, ethyl-thiazolylmethyl, methyl-thiazolylethyl, imidazolylmethyl, methyl-imidazolylmethyl, ethyl-imidazolylmethyl, benzyl-imidazolylmethyl, benzimidazolylmethyl, methyl-oxadiazolylmethyl, triazolylmethyl, methyl-triazolylmethyl, propyl-triazolylmethyl, benzyl-triazolylmethyl, pyridinylmethyl-triazolylmethyl, cyanomethyl-triazolylmethyl, dimethylaminomethyl-triazolylmethyl, aminoethyl-triazolylmethyl, dimethylaminoethyl-triazolylmethyl, dimethylaminocarbonylmethyl-triazolylmethyl, *N*-methylpiperidinyl-triazolylmethyl, pyrrolidinylethyl-triazolylmethyl, piperazinylethyl-triazolylmethyl, morpholinylethyl-triazolylmethyl, methyl-tetrazolylmethyl, pyridinylmethyl, methyl-pyridinylmethyl, dimethyl-pyridinylmethyl, ethoxy-pyridinylmethyl, cyclopropylmethoxy-pyridinylmethyl, pyridazinylmethyl, chloro-pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

A favoured value of R^2 is methyl-triazolylmethyl.

A particular sub-class of compounds of use in the invention is represented by the compounds of formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein R^1 is as defined above;

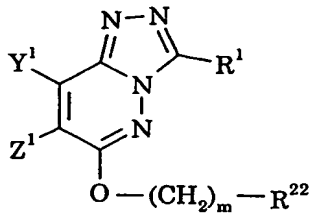
n is 1, 2, 3 or 4, typically 1; and

R^{12} represents hydroxy; or C_{3-7} cycloalkyl, C_{3-7} heterocycloalkylcarbonyl, aryl or heteroaryl, any of which groups may be optionally substituted.

Examples of optional substituents on the group R^{12} suitably include C_{1-6} alkyl, aryl(C_{1-6})alkyl, halogen, cyano, hydroxymethyl, C_{1-6} alkoxy and C_{3-7} cycloalkyl(C_{1-6})alkoxy. Typical substituents include methyl, ethyl, benzyl, chloro, cyano, hydroxymethyl, ethoxy and cyclopropylmethoxy.

Particular values of R^{12} include hydroxy, hydroxymethyl-cyclohexyl, pyrrolidinylcarbonyl, cyanophenyl, hydroxymethyl-phenyl, pyrazolyl, dimethylpyrazolyl, thiazolyl, methylthiazolyl, ethylthiazolyl, imidazolyl, methylimidazolyl, ethylimidazolyl, benzylimidazolyl, methyltriazolyl, pyridinyl, methylpyridinyl, dimethyl-pyridinyl, ethoxypyridinyl, cyclopropylmethoxy-pyridinyl, pyridazinyl, chloropyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and quinoxalinyl.

Another sub-class of compounds of use in the invention is represented by the compounds of formula IIB, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIB)

wherein

Y^1 represents hydrogen or methyl;

Z^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally substituted;

R^1 is as defined with reference to formula I above;

m is 1 or 2, preferably 1; and

R^{22} represents aryl or heteroaryl, either of which groups may be optionally substituted.

Suitably, Y^1 represents hydrogen.

Examples of typical substituents on the group Z^1 include C_{1-6} alkyl and halogen, especially methyl or chloro.

Representative values for the group Z^1 include methyl, ethyl, isopropyl, *tert*-butyl, 1,1-dimethylpropyl, methyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, cyclobutenyl, phenyl, pyrrolidinyl, methyl-pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyridinyl, furyl, thienyl, chloro-thienyl and diethylamino.

A favoured value of Z^1 is cyclobutyl.

Examples of typical substituents on the group R^{22} include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, cyano, cyano(C_{1-6})alkyl, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, di(C_{1-6})alkylamino(C_{1-6})alkyl, amino(C_{1-6})alkyl,

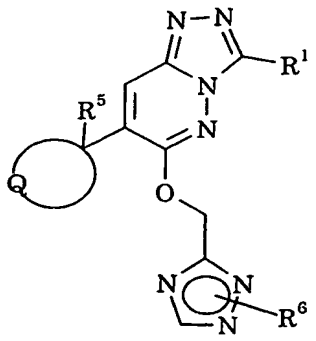
di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl and morpholinyl(C_{1-6})alkyl.

Illustrative values of specific substituents on the group R^{22} include methyl, ethyl, *n*-propyl, benzyl, pyridinylmethyl, chloro, cyano, cyanomethyl, hydroxymethyl, ethoxy, cyclopropylmethoxy, dimethylaminomethyl, aminoethyl, dimethylaminoethyl, dimethylaminocarbonylmethyl, *N*-methylpiperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylmethyl.

Particular values of R^{22} include cyanophenyl, hydroxymethyl-phenyl, pyrazolyl, dimethyl-pyrazolyl, methyl-isoxazolyl, thiazolyl, methyl-thiazolyl, ethyl-thiazolyl, imidazolyl, methyl-imidazolyl, ethyl-imidazolyl, benzyl-imidazolyl, benzimidazolyl, methyl-oxadiazolyl, triazolyl, methyl-triazolyl, propyl-triazolyl, benzyl-triazolyl, pyridinylmethyl-triazolyl, cyanomethyl-triazolyl, dimethylaminomethyl-triazolyl, aminoethyl-triazolyl, dimethylaminoethyl-triazolyl, dimethylaminocarbonylmethyl-triazolyl, *N*-methylpiperidinyl-triazolyl, pyrrolidinylethyl-triazolyl, piperazinylethyl-triazolyl, morpholinylethyl-triazolyl, methyl-tetrazolyl, pyridinyl, methyl-pyridinyl, dimethyl-pyridinyl, ethoxy-pyridinyl, cyclopropylmethoxy-pyridinyl, pyridazinyl, chloro-pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and quinoxalinyl.

A favoured value of R^{22} is methyl-triazolyl.

A particular subset of the compounds of formula IIB above of use in the present invention is represented by the compounds of formula IIC, and pharmaceutically acceptable salts thereof:



(IIC)

wherein

R^1 is as defined with reference to formula I above;

Q represents the residue of a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring;

R^5 represents hydrogen or methyl; and

R^6 represents hydrogen or methyl.

In relation to formula IIC above, R^1 suitably represents phenyl.

In a favoured embodiment, Q suitably represents the residue of a cyclobutyl ring.

Suitably, R^5 represents hydrogen.

Suitably, R^6 represents methyl.

Specific compounds of use in the present invention include:

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3,7-diphenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

7,8-dimethyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7,8-benzo-3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

8-methyl-3,7-diphenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-methano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-5-(pyridin-2-ylmethoxy)-1,2,3a,4,7-pentaazacyclopenta-[*a*]naphthalene;

3-phenyl-5-(pyridin-2-ylmethoxy)-1,2,3a,4,8-pentaazacyclopenta-[*a*]naphthalene;

8-methyl-3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-pyridyl)methyloxy-(7,8-pentano)-1,2,4-triazolo[4,3-b]pyridazine;

8,8-dimethyl-3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-7-(piperidin-1-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(pyridin-4-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-5-(pyridin-2-ylmethoxy)-6,7,8,9-tetrahydro-1,2,3a,4,8-pentaaza-cyclopenta[*a*]naphthalene;

3-phenyl-5-(pyridin-2-ylmethoxy)-6,7,8,9-tetrahydro-1,2,3a,4,7-pentaaza-cyclopenta[*a*]naphthalene;

7-methyl-3-phenyl-5-(pyridin-2-ylmethoxy)-6,7,8,9-tetrahydro-1,2,3a,4,7-pentaazacyclopenta[*a*]naphthalene;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-propano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(4-methyl)phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(3-methoxy)phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(2-fluoro)phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(3-pyridyl)-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-cyclopropyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(6-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(3-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(4-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(5-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(4-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-[2-(1-methyl)imidazolyl]methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(3-cyanophenyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[1-(3,5-dimethyl)pyrazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[4-(2-methyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-quinoxalinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-pyridazinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-benzylimidazol-2-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(isoquinolin-1-yl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-ethylimidazol-2-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(1-pyrazolyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(*N*-pyrrolidinylcarbonyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[4-(3-methyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-quinolinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(2-imidazolyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-thiazolyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(5-methyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(4-methyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(3,5-dimethyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-pyrazinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(4,6-dimethyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(4-thiazolyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(5,6-dimethyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-methylimidazol-2-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(4-pyrimidinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[4-(2-ethyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(6-chloropyridazin-3-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(2-imidazolyl)methyloxy-3-(4-methylphenyl)-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-hydroxymethylphenyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-hydroxybutyl)oxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-hydroxymethylcyclohexyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(3-hydroxymethylphenyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-methyl-1,2,4-triazol-3-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(2-methyl-1,2,4-triazol-3-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-cyclopropylmethyloxy-2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-ethoxy-2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(6-methylpyridin-2-yl)methyloxy-3-phenyl-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-tetrazol-5-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]-pyridazine;

3,7-diphenyl-6-(2-propyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(1-propyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-imidazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-3*H*-imidazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(4-methyl-4*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-3*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methoxyphenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-7-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(morpholin-4-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(pyridin-3-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclohexyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclohexyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-3-phenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(pyridin-2-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2,4-difluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(pyridin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2,4-difluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-phenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-7-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-6-(3-methylpyridin-2-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-ethyl-1*H*-imidazol-2-ylmethoxy)-3-(4-methylphenyl)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiomorpholin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-[2-(4-methylthiazol-5-yl)ethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

(±)-7-(2-methylpyrrolidin-1-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyridin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-isopropyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-cyclopropyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(pyridin-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(pyridin-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-3-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methyl-1,2,4-oxadiazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-phenyl-3-(thiophen-2-yl)-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(thiophen-3-yl)-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(2*H*-1,2,3-triazol-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrazin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(4-methylthiazol-2-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methylthiazol-2-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrimidin-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyridazin-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(thiazol-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methylisoxazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(3-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrimidin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-isopropyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(4-methoxyphenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(furan-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-ylacetonitrile;

7-(1-methylcyclopropyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopropyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(3-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(5-methylthiophen-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]-*N*,*N*-dimethylacetamide;

3,7-diphenyl-6-[1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-benzyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

2-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]acetamide;

N-[2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]ethyl]-*N*,*N*-dimethylamine;

3,7-diphenyl-6-(pyrimidin-5-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-[1-(2-(morpholin-4-yl)-ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(5-chlorothiophen-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(5-chlorothiophen-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1*H*-benzimidazol-2-ylmethoxy)-3-(2,4-difluorophenyl)-7-(1-methylcyclopentyl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-3-yl)-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

7-cyclobutyl-3-phenyl-6-(prop-2-ynyloxy)-1,2,4-triazolo[4,3-b]pyridazine;

(7-cyclobutyl-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxy)acetonitrile;

N-[4-(7-cyclobutyl-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxy)but-2-ynyl]-*N*,*N*-dimethylamine;

2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]ethylamine;

3,7-diphenyl-6-[1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

6-[1-(1-methylpiperidin-4-yl)-1*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-[1-(2-(piperazin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2,4-difluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(cyclobut-1-enyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-3-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

N,*N*-diethyl-*N*-[6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-7-yl]amine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2,4-difluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1,1-dimethylpropyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(4-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(4-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-8-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-[4-(2,6-dimethylmorpholin-4-yl)but-2-ynyloxy]-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

and pharmaceutically acceptable salts thereof and prodrugs thereof.

In another aspect, the present invention provides a method for the treatment and/or prevention of psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity (e.g. in paraplegic patients); with substantially no sedation, which comprises administering to a patient in need of such treatment an effective amount of a compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the α3 subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

This aspect of the present invention also provides the use of a compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the α3 subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human

$GABA_A$ receptor, for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity (e.g. in paraplegic patients); with substantially no sedation.

In this aspect of the invention, the binding affinity (K_i) of compounds for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of compounds of use in this aspect of the invention is 10 nM or less, preferably 2 nM or less, and more preferably 1 nM or less.

In this aspect of the invention, the potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk^- fibroblast cells.

The compounds of use in this aspect of the invention will elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of use in this aspect of the invention will elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

In order to elicit their behavioural effects, the compounds of use in this aspect of the invention will be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of use in this aspect of the invention will be

capable of exerting their beneficial therapeutic action following administration by the oral route.

A representative compound of use in this aspect of the invention is 7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine.

For therapeutic application, pharmaceutical compositions may be provided which comprise one or more compounds of use in this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of use in the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can

comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

Pharmaceutical compositions in liquid form may be adapted for administration orally or by injection and may include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of schizophrenia, neurodegeneration arising from cerebral ischemia, pain, emesis, and muscle spasm or spasticity, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

If desired, the compounds of use in this invention may be co-administered with another anti-schizophrenic medicament, for example one producing its effects *via* dopamine D_2 and/or 5-HT_2 receptor blockade. In such circumstances, an enhanced anti-schizophrenic effect may be envisaged without a corresponding increase in sedation and/or extrapyramidal side-effects (movement disorders) such as may be caused by, for example, D_2 receptor subtype blockade; or a comparable anti-schizophrenic effect with reduced side-effects may alternatively be envisaged. Such co-administration may be desirable where a patient is

already established on a treatment regime involving conventional anti-schizophrenic medicaments. Suitable anti-schizophrenic medicaments of use in combination with the compounds according to the present invention include haloperidol, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chloroprothixene, thiothixene, clozapine, olanzapine, pimozide, molindone, loxapine, sulpiride, risperidone, xanomeline, fananserin and ziprasidone, and pharmaceutically acceptable salts thereof.

If desired, the compounds of use in this invention may be co-administered with another neuroprotective medicament, for example a compound which is active as an antagonist of the strychnine-insensitive glycine modulatory site of the N-methyl-D-aspartate (NMDA) receptor (a "glycine/NMDA antagonist"); or a compound which modulates glutamatergic transmission such as riluzole. Typical glycine/NMDA antagonists are described in, for example, EP-A-0481676.

If desired, the compounds of use in this invention may be co-administered with another analgesic medicament, for example a non-steroidal anti-inflammatory drug (NSAID) or an opioid analgesic. Specific NSAIDs include aspirin, paracetamol (acetaminophen), diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Specific opioid analgesics include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. A particular opioid analgesic is morphine. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol

tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Preferably, the compounds of use in this invention may be co-administered with a compound which is a selective inhibitor of cyclooxygenase-2 (COX-2) relative to cyclooxygenase-1 (COX-1). Such compounds are conventionally referred to in the art as "selective COX-2 inhibitors". Preferred selective COX-2 inhibitors include rofecoxib, celecoxib and meloxicam; preferably rofecoxib, which is 3-phenyl-4-(4-methylsulfonylphenyl)-2-(5H)-furanone.

If desired, the compounds of use in this invention may be co-administered with another anti-emetic medicament, for example a 5-HT_3 antagonist such as ondansetron, granisetron or tropisetron; a dopamine antagonist such as metoclopramide or domperidone; an anticholinergic agent such as scopolamine; a $GABA_B$ receptor agonist such as baclofen; or a tachykinin NK_1 receptor antagonist as described, for example, in EP-A-0436334, EP-A-0443132, EP-A-0532456, EP-A-0591040, WO 92/17449, WO 93/21155, WO 95/08549, WO 95/14017, WO 95/16679, WO 95/18124, WO 95/23798, or copending international patent application no. PCT/GB97/01630 (published on 31 December 1997 as WO 97/49710).

If desired, the compounds of use in this invention may be co-administered with another muscle relaxant agent such as baclofen.

The compounds of formula I of use in the present invention, including the specific compounds disclosed above, may be prepared by the processes described in WO 98/04559.

The compounds of use in this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the $\alpha 2$ or $\alpha 3$ subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for $\alpha1\beta3\gamma2$ cells; 18 nM for $\alpha2\beta3\gamma2$ cells; 10 nM for $\alpha3\beta3\gamma2$ cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 μl of assay buffer.
- 50 μl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM).
- 50 μl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 μM final concentration.
- 100 μl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000

dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The specific compounds listed above were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-flumazenil from the α2 and/or α3 subunit of the human $GABA_A$ receptor of 100 nM or less.

The present invention also provides a pharmaceutical product comprising (i) a compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the α3 subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human $GABA_A$ receptor; and (ii) a tachykinin NK_1 receptor antagonist; for simultaneous, separate or sequential administration.

The $GABA_A$ receptor agonists of use in this aspect of the invention will elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the $GABA_A$ receptor agonists of use in this aspect of the invention will elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The present invention also provides a pharmaceutical product comprising (i) a compound of formula I as defined above, or a

pharmaceutically acceptable salt thereof or a prodrug thereof; and (ii) a tachykinin NK_1 receptor antagonist; for simultaneous, separate or sequential administration.

The preferred compounds of formula I for use in these pharmaceutical products are the same as the preferred compounds of formula I disclosed herein for use in emesis.

The preferred tachykinin NK_1 receptor antagonists for use in these pharmaceutical products are those described in EP-A-0436334, EP-A-0443132, EP-A-0532456, EP-A-0591040, WO 92/17449, WO 93/21155, WO 95/08549, WO 95/14017, WO 95/16679, WO 95/18124, WO 95/23798 and WO 97/49710 (published on 31 December 1997 and corresponding to international patent application no. PCT/GB97/01630).

To determine whether the compounds of use in the present invention have a potential use as non-sedating analgesics, a study has been carried out to examine the antinociceptive effects of 6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine (hereinafter referred to as "Compound A") in the rat carrageenan-induced hyperalgesia assay, a robust test of inflammatory pain in which COX-2 inhibitors have been shown to be active, and to compare these effects with its ability to induce sedation in rats as measured by disruption of chain pulling.

Methods

Carrageenan-induced hyperalgesia

Male Sprague Dawley rats (100-120 g) received an intraplantar injection of carrageenan (4.5 mg) and mechanical thresholds were determined 3 h later using a modified Ugo Basile Algesiometer. Control rats received saline (0.15 ml i.pl.). Hyperalgesia was defined as the difference in vocalisation threshold for saline- and carrageenan-injected rats. Paw pressure scores for drug-treated rats were expressed as a

percentage of this response. Compound A (1, 3 or 10 mg/kg) or vehicle were administered 2 h after carrageenan.

Chain pulling

Response sensitivity training and testing was carried out in standard operant conditioning chambers. Each chamber was equipped with a chain suspended from the centre of the ceiling and connected to a micro switch. Food pellets were delivered into a food magazine positioned at floor level in the centre of the front wall. Food-deprived P.V.G. rats (280-380 g) were trained to pull a chain for access to food pellets according to a random interval (RI) 30 s schedule. Animals received Compound A at 1, 3, 10, 30 or 100 mg/kg or vehicle and the number of chain pulls recorded for up to 60 min. Response rates for drug-treated animals are then expressed as a percentage of response rates for vehicle-treated rats.

Compound A was suspended in 0.5% methocel and administered orally. Doses refer to the free base.

Results

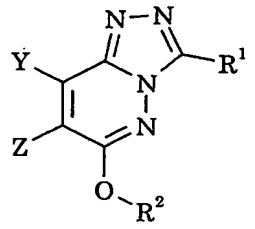
Intraplantar injection of carrageenan induced marked paw oedema and hyperalgesia to mechanical compression of the inflamed paw. Oral administration of Compound A inhibited carrageenan-induced hyperalgesia (ID_{50} 5.3 mg/kg p.o.; Figure 1). In contrast, Compound A had no effects on chain pulling at doses of up to 100 mg/kg (Figure 1).

Conclusions

These findings demonstrate that Compound A possesses antinociceptive activity without causing sedation, confirming that the compounds of use in the present invention are effective non-sedating analgesics.

CLAIMS:

1. A method for the treatment and/or prevention of psychotic disorders; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity; which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



(I)

wherein

Y represents hydrogen or C_{1-6} alkyl; and

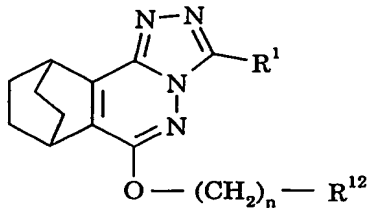
Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or

Y and Z are taken together with the two intervening carbon atoms to form a ring selected from C_{5-9} cycloalkenyl, C_{6-10} bicycloalkenyl, tetrahydropyridinyl, pyridinyl and phenyl, any of which rings may be optionally benzo-fused and/or substituted;

R^1 represents C_{3-7} cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted; and

R^2 represents cyano(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, propargyl, C_{3-7} heterocycloalkylcarbonyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

2. A method according to claim 1 wherein the compound administered is represented by formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



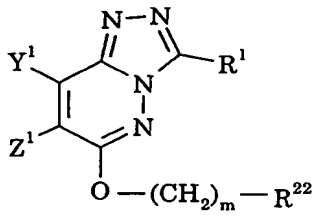
(IIA)

wherein R^1 is as defined in claim 1;

n is 1, 2, 3 or 4; and

R^{12} represents hydroxy; or C_{3-7} cycloalkyl, C_{3-7} heterocycloalkylcarbonyl, aryl or heteroaryl, any of which groups may be optionally substituted.

3. A method according to claim 1 wherein the compound administered is represented by formula IIB, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIB)

wherein

Y^1 represents hydrogen or methyl;

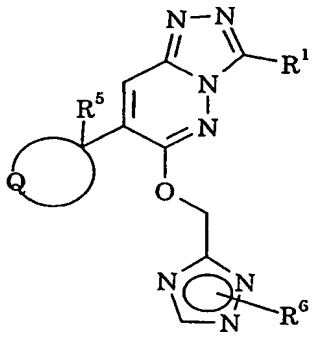
Z^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl or di(C_{1-6})alkylamino, any of which groups may be optionally substituted;

R^1 is as defined in claim 1;

m is 1 or 2; and

R^{22} represents aryl or heteroaryl, either of which groups may be optionally substituted.

4. A method according to claim 3 wherein the compound administered is represented by formula IIC, and pharmaceutically acceptable salts thereof:



(IIC)

wherein

R^1 is as defined in claim 1;

Q represents the residue of a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring;

R^5 represents hydrogen or methyl; and

R^6 represents hydrogen or methyl.

5. A method according to claim 1 wherein the compound administered is selected from:

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3,7-diphenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

7,8-dimethyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

7,8-benzo-3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

8-methyl-3,7-diphenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-methano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-5-(pyridin-2-ylmethoxy)-1,2,3a,4,7-pentaazacyclopenta-[*a*]naphthalene;

3-phenyl-5-(pyridin-2-ylmethoxy)-1,2,3a,4,8-pentaazacyclopenta-[*a*]naphthalene;

8-methyl-3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-pyridyl)methyloxy-(7,8-pentano)-1,2,4-triazolo[4,3-b]pyridazine;

8,8-dimethyl-3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-7-(piperidin-1-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(pyridin-4-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-5-(pyridin-2-ylmethoxy)-6,7,8,9-tetrahydro-1,2,3a,4,8-pentaaza-cyclopenta[*a*]naphthalene;

3-phenyl-5-(pyridin-2-ylmethoxy)-6,7,8,9-tetrahydro-1,2,3a,4,7-pentaaza-cyclopenta[*a*]naphthalene;

7-methyl-3-phenyl-5-(pyridin-2-ylmethoxy)-6,7,8,9-tetrahydro-1,2,3a,4,7-pentaazacyclopenta[*a*]naphthalene;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-propano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(4-methyl)phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(3-methoxy)phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(2-fluoro)phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-(3-pyridyl)-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-cyclopropyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(6-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(3-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(4-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[(5-methyl)-2-pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(4-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-[2-(1-methyl)imidazolyl]methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(3-cyanophenyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[1-(3,5-dimethyl)pyrazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[4-(2-methyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-quinoxalinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-pyridazinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-benzylimidazol-2-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(isoquinolin-1-yl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-ethylimidazol-2-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(1-pyrazolyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(*N*-pyrrolidinylcarbonyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[4-(3-methyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-quinolinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(2-imidazolyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-thiazolyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(5-methyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(4-methyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(3,5-dimethyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(2-pyrazinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(4,6-dimethyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(4-thiazolyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[2-(5,6-dimethyl)pyridyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-methylimidazol-2-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(4-pyrimidinyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-[4-(2-ethyl)thiazolyl]methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(6-chloropyridazin-3-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(2-imidazolyl)methyloxy-3-(4-methylphenyl)-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-hydroxymethylphenyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-hydroxybutyl)oxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(4-hydroxymethylcyclohexyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(3-hydroxymethylphenyl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-methyl-1,2,4-triazol-3-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(2-methyl-1,2,4-triazol-3-yl)methyloxy-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-cyclopropylmethyloxy-2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

3-phenyl-6-(3-ethoxy-2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine;

6-(6-methylpyridin-2-yl)methyloxy-3-phenyl-1,2,4-triazolo[3,4-a]phthalazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-tetrazol-5-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]-pyridazine;

3,7-diphenyl-6-(2-propyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(1-propyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-imidazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-3*H*-imidazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(4-methyl-4*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-3*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methoxyphenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-7-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(morpholin-4-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(pyridin-3-yl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclohexyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclohexyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-ethyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclobutyl-3-phenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(pyridin-2-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2,4-difluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(pyridin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2-fluorophenyl)-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(2,4-difluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-phenyl-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-7-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-6-(3-methylpyridin-2-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-ethyl-1*H*-imidazol-2-ylmethoxy)-3-(4-methylphenyl)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-6-(pyridin-2-ylmethoxy)-7-(thiomorpholin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-[2-(4-methylthiazol-5-yl)ethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

(±)-7-(2-methylpyrrolidin-1-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyridin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-isopropyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-cyclopropyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(pyridin-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(pyridin-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-3-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methyl-1,2,4-oxadiazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-phenyl-3-(thiophen-2-yl)-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-phenyl-7-(thiophen-3-yl)-6-(2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(2*H*-1,2,3-triazol-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrazin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(4-methylphenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(4-methylthiazol-2-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methylthiazol-2-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrimidin-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyridazin-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(thiazol-4-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(5-methylisoxazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(3-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-(morpholin-4-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-(pyrimidin-2-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-isopropyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-*tert*-butyl-3-(2-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(4-methoxyphenyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(furan-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

7-cyclopentyl-3-(furan-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-ylacetonitrile;

7-(1-methylcyclopropyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopropyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(3-fluorophenyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,3-triazol-4-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3-(5-methylthiophen-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-7-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]-*N*,*N*-dimethylacetamide;

3,7-diphenyl-6-[1-(pyridin-2-ylmethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-benzyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

2-[5-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]acetamide;

N-[2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]ethyl]-*N*,*N*-dimethylamine;

3,7-diphenyl-6-(pyrimidin-5-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-[1-(2-(morpholin-4-yl)-ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(5-chlorothiophen-2-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(5-chlorothiophen-2-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(1*H*-benzimidazol-2-ylmethoxy)-3-(2,4-difluorophenyl)-7-(1-methylcyclopentyl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(furan-3-yl)-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]phthalazine;

7-cyclobutyl-3-phenyl-6-(prop-2-ynyloxy)-1,2,4-triazolo[4,3-b]pyridazine;

(7-cyclobutyl-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxy)acetonitrile;

N-[4-(7-cyclobutyl-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxy)but-2-ynyl]-*N*,*N*-dimethylamine;

2-[3-(3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazin-6-yloxymethyl)-1,2,4-triazol-1-yl]ethylamine;

3,7-diphenyl-6-[1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

6-[1-(1-methylpiperidin-4-yl)-1*H*-1,2,4-triazol-3-ylmethoxy]-3,7-diphenyl-1,2,4-triazolo[4,3-b]pyridazine;

3,7-diphenyl-6-[1-(2-(piperazin-1-yl)ethyl)-1*H*-1,2,4-triazol-3-ylmethoxy]-1,2,4-triazolo[4,3-b]pyridazine;

7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2,4-difluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(cyclobut-1-enyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

7-(furan-3-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

N,N-diethyl-*N*-[6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazin-7-yl]amine;

7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2,4-difluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;

7-(1,1-dimethylpropyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(4-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(4-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

3-(2-fluorophenyl)-7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-b]pyridazine;

6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-7-(thiophen-3-yl)-1,2,4-triazolo[4,3-b]pyridazine;

8-methyl-7-(1-methylcyclobutyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
8-methyl-7-(1-methylcyclobutyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine;
7-cyclobutyl-8-methyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
7-cyclobutyl-8-methyl-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
7-(1-methylcyclopentyl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;
7-(1-methylcyclopentyl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine;
7-cyclobutyl-6-[4-(2,6-dimethylmorpholin-4-yl)but-2-ynyloxy]-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine;
and pharmaceutically acceptable salts thereof and prodrugs thereof.

6. A method for the treatment and/or prevention of psychotic disorders; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity; with substantially no sedation, which comprises administering to a patient in need of such treatment an effective amount of a compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the $\alpha 3$ subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the $\alpha 3$ subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the $\alpha 1$ subunit of the human $GABA_A$ receptor.

7. A method for the treatment and/or prevention of psychotic disorders; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity; which comprises administering to a patient in need of such treatment an effective amount of 7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine.

8. The use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof, for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity.

9. The use as claimed in claim 8 of a compound of formula IIA as defined in claim 2, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

10. The use as claimed in claim 8 of a compound of formula IIB as defined in claim 3, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

11. The use as claimed in claim 10 of a compound of formula IIC as defined in claim 4, or a pharmaceutically acceptable salt thereof.

12. The use as claimed in claim 8 of a compound specifically recited in claim 5, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

13. The use of a compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the $\alpha 3$ subunit of the human $GABA_A$ receptor of 10

nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human $GABA_A$ receptor, for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity; with substantially no sedation.

14. The use of 7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-b]pyridazine for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders; neurodegeneration arising from cerebral ischemia; pain; emesis; and muscle spasm or spasticity.

15. A pharmaceutical composition comprising a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof, in association with a further antipsychotic, neuroprotective, analgesic, antiemetic or muscle relaxant medicament.

16. A composition as claimed in claim 15 wherein the further antipsychotic medicament is selected from haloperidol, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chloroprothixene, thiothixene, clozapine, olanzapine, pimozide, molindone, loxapine, sulpiride, risperidone, xanomeline, fananserin and ziprasidone, and pharmaceutically acceptable salts thereof.

17. A composition as claimed in claim 15 wherein the further neuroprotective medicament is an antagonist of the strychnine-insensitive

glycine modulatory site of the N-methyl-D-aspartate receptor; or a modulator of glutamatergic transmission.

18. A composition as claimed in claim 15 wherein the further analgesic medicament is a non-steroidal anti-inflammatory drug or an opioid analgesic.

19. A composition as claimed in claim 15 wherein the further analgesic medicament is a selective COX-2 inhibitor.

20. A composition as claimed in claim 19 wherein the selective COX-2 inhibitor is rofecoxib, celecoxib or meloxicam.

21. A composition as claimed in claim 20 wherein the selective COX-2 inhibitor is rofecoxib.

22. A composition as claimed in claim 15 wherein the further antiemetic medicament is selected from a 5-HT_3 antagonist; a dopamine antagonist; an anticholinergic agent; a $GABA_A$ receptor agonist; and a tachykinin NK_1 antagonist.

23. A pharmaceutical composition comprising a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof, in association with a tachykinin NK_1 receptor antagonist.

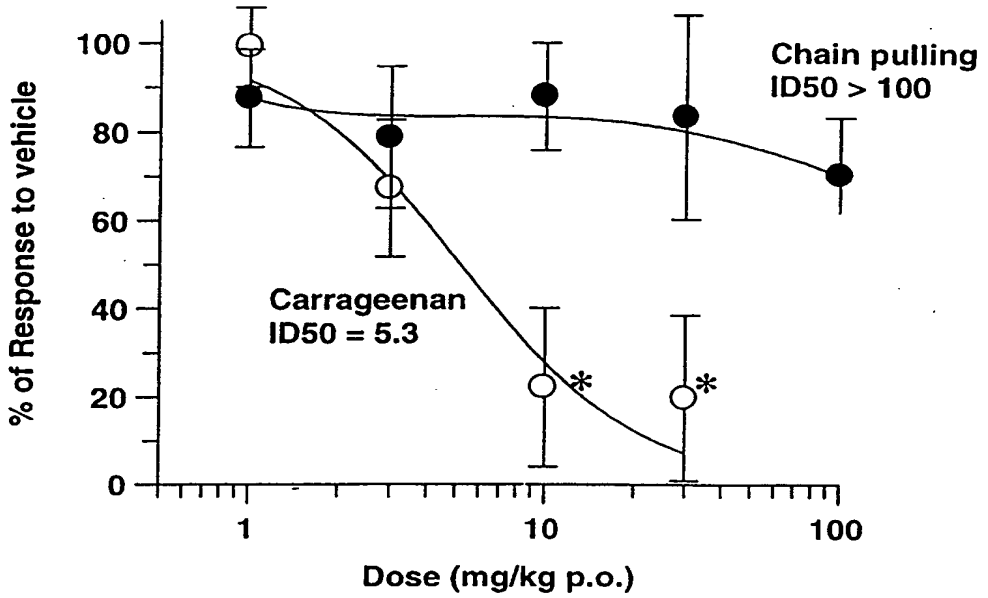
24. A pharmaceutical product comprising (i) a compound which is a modulator of the benzodiazepine binding site of the human $GABA_A$ receptor, having a binding affinity (K_i) for the $\alpha 3$ subunit of the human $GABA_A$ receptor of 10 nM or less, which elicits at least a 40% potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines

expressing the α3 subunit of the human $GABA_A$ receptor, and which elicits at most a 30% potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α1 subunit of the human $GABA_A$ receptor; and (ii) a tachykinin NK_1 receptor antagonist; for simultaneous, separate or sequential administration.

25. A pharmaceutical product comprising (i) a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof; and (ii) a tachykinin NK_1 receptor antagonist; for simultaneous, separate or sequential administration.

26. A composition as claimed in claim 15 wherein the further muscle relaxant medicament is baclofen.

Figure 1



* p<0.05 compared to carrageenan-vehicle treated rats

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 98/03328

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/50 A61K31/00 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 04559 A (GUIBLIN ALEXANDER RICHARD ;MERCK SHARP & DOHME (GB); MOORE KEVIN W) 5 February 1998 see abstract see page 3, line 3 - line 27 see page 4, line 12 - page 5, line 2 see page 33, line 16 - page 35, line 30; claims; examples ---	1-14
P,X	WO 98 34923 A (MERCK SHARP & DOHME ;HARRISON TIMOTHY (GB); SPAREY TIMOTHY JASON () 13 August 1998 see abstract see page 3, line 17 - page 4, line 8 see page 4, line 20 - page 5, line 8 see page 11, line 11 - line 30 --- -/--	6,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 1999	23/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

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INTERNATIONAL SEARCH REPORT

Inter hal Application No
PCT/GB 98/03328

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	E.D. HALL ET AL.: "NEUROPROTECTIVE PROPERTIES OF THE BENZODIAZEPINE RECEPTOR PARTIAL AGONIST PNU-101017 IN THE GERBIL FOREBRAIN ISCHEMIA MODEL" JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, vol. 17, no. 8, August 1997, pages 875-883, XP002096057 cited in the application	6,13
Y	see the whole document	1,8
X	A. DELINI-STULA ET AL.: "ANTIPSYCHOTIC EFFECTS OF BRETAZENIL, A PARTIAL BENZODIAZEPINE AGONIST IN ACUTE SCHIZOPHRENIA-A STUDY GROUP REPORT" JOURNAL OF PSYCHIATRIC RESEARCH, vol. 30, no. 4, 1996, pages 239-250, XP002096058 cited in the application	6,13
Y	see the whole document	1,8
A	HADINGHAM K L ET AL: "CLONING OF CDNA SEQUENCES ENCODING HUMAN ALPHA2 AND ALOHA3 GAMMA- AMINOBUTYRIC ACIDA RECEPTOR SUBUNITS AND CHARACTERIZATION OF THE BENZODIAZEPINE PHARMACOLOGY OF RECOMBINANT APLHA1-, ALPHA2-, ALPHA3-, AND ALPHA5-CONTAINING HUMAN GAMMA-AMINOBUTYRIC ACIDA RECEPTORS" MOLECULAR PHARMACOLOGY, vol. 43, 1 January 1993, pages 970-975, XP000569554 see the whole document, in particular table 1	6,13
X,Y	EP 0 085 840 A (LEPETIT SPA) 17 August 1983 see abstract see page 5, line 4 - line 19; examples 102,103 see page 61, line 1 - page 66, line 12; claims	1,6,8,13
X,Y	TARZIA G ET AL: "BENZODIAZEPINE RECEPTOR LIGANDS. SYNTHESIS AND PRELIMINARY PHARMACOLOGICAL EVALUATION OF SOME 3-ARYL-6-THIOALKYL-, 3-ARYL-6-ALKYLSULPHINYL-, 3-ARYL-6-ALKYLSULPHONYL-, AND 3-ARYL-6-ALKOXY-1,2,4-TRIAZOLO 3,4-APHTHALAZINES" FARMACO, EDIZIONE SCIENTIFICA, vol. 43, no. 2, February 1988, pages 189-201, XP002041885 see the whole document	1,6,8,13

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INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 98/03328

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	E. DUNN ET AL.: "DIFFERENTIAL DISTRIBUTION OF GABAA RECEPTOR SUBUNITS IN THE RAT INFRALIMBIC CORTEX: RELEVANCE TO NOVEL ANTIPSYCHOTIC DRUG TREATMENT" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 21, no. 1-3, 1995, page 2046 XP002096059 see abstract 804.6 ---	1,6,8,13
A	WO 96 32393 A (KNOLL AG ;SARGENT BRUCE JEREMY (GB); FERNANDEZ FERNANDEZ MARIA ISA) 17 October 1996 see abstract see page 1, line 1 - line 9 see page 15, line 20 - line 31 see page 16, line 23 - line 32; claims; examples ---	1-26
A	DE 196 17 862 A (SCHERING AG) 30 October 1997 see abstract see page 3, line 37 - line 50; claims; examples 3,4 ---	1-26
A	EP 0 156 734 A (SANOFI SA) 2 October 1985 see abstract see examples see page 15, line 4 - line 8; claims ---	1-26
A	CHEMICAL ABSTRACTS, vol. 89, no. 5, 31 July 1978 Columbus, Ohio, US; abstract no. 43471, "S-TRIAZOLO(3,4-a)(5,6,7,8)TETRAHYDROPHTHALAZINES" XP002096060 see abstract & JP 53 021197 A (MITSUBISHI CHEMICAL IND.) 27 February 1978 -----	1-26

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03328

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically contained within the definition of claims 6,13 and 24, the search had to be restricted for economic reasons. The search was limited to the general idea of the invention and to the compounds of formula (I) (Article 6 PCT; Guidelines, Chapt.II.7 last sentence and Chapt.III,3.7).

Claims searched completely: 1-5,7-12,14-23,25,26

Claims searched incompletely: 6,13,24

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern hal Application No
PCT/GB 98/03328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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